In the Specification:

Please replace pages 1-52 of the specification with the substitute specification, pages 1-54, provided herewith. A marked-up copy of the specification has been submitted herewith.

In the claims:

Please cancel claims 1-15, 17, 19, and 26-29, without prejudice, and amend claims 16 and 18 as follows:

16. **(Amended)** A method of identifying a species which is an agonist or antagonist of $cPLA_2$ activity or binding comprising: (a) providing a model of the structure of $cPLA_2$ comprising a data set embodying the structure of $cPLA_2$ (b) studying the interaction of candidate species with such model, and (c) selecting a species which is predicted to act as said agonist or antagonist.

18. **(Amended)** A process of identifying a substance that inhibits $cPLA_2$ activity or membrane binding comprising determining the interaction between a candidate substance and a model of the structure of $cPLA_2$.

REMARKS

Claims were 1-29 were pending in the application. Claims 1-15, 17, 19, and 26-29 have been cancelled without prejudice and claims 16 and 18 have been amended. Accordingly, after the amendments presented herein have been entered, claims 16, 18, and 20-25 will be pending in the instant application. For the Examiner's convenience, the pending claims are set forth in Appendix A.

Applicants submit herewith a "Version with Markings to Show Changes Made," which indicates the specific amendments made to the specification and the claims. *No new matter has been added.*

Support for the amendments to claims 16 and 18 can be found throughout the specification and claims as originally filed.

Any amendments to the claims are not to be construed as an acquiescence to any of the rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Objections to the Specification

The Examiner has indicated that "the substitute specification filed on September 5, 2000 has not been entered because it does not conform to 37 CFR 1.125(b) because: a marked up copy of the specification was not received."

Applicants submit herewith another substitute specification under 37 C.F.R. §1.125(a), along with a marked-up copy of the specification. This substitute specification contains only the subject matter from the original specification. References to sequences contained in the Sequence Listing, filed on September 5, 2000, have been inserted throughout the specification. In addition, the title of the application has been inserted on the first page of the specification, the pages have been renumbered, and minor typographical errors have also been corrected.

A paragraph has been inserted into the specification which incorporates by reference the contents of the file named "Table 2.txt" which is contained on the CD-R filed, in duplicate, herewith. The file entitled "Table 2.txt" contains the structural coordinates of cytosolic phospholipase A_2 ($cPLA_2$). Reference to Table 2 has also been inserted into the specification at page 41. No new matter has been added to the specification. Applicants respectfully request that the Examiner enter this substitute specification.

Rejection of Claims 16, 18, and 20-25 Under 35 U.S.C. §112, first paragraph

Claims 16, 18, and 20-25 have been rejected under 35 U.S.C. §112, first paragraph because, according to the Examiner, claims 16, 18, and 20-25 "contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." In particular, the Examiner is of the opinion that

> A necessary, but not sufficient, condition to practice the invention of claims 16, 18 and 20-25 is $cPLA_2$ of sufficient purity that a molecular model can be obtained. In the instant specification it is suggested that an x-ray crystallographic model can be generated. Therefore, the specification must present an enabling disclosure for how to obtain $cPLA_2$ preparations amenable to crystallization. The purported purification procedure for $cPLA_2$ is set forth at pages 35-36 of the specification. However, the specification affords no specific sequence of steps to permit the isolation of $cPLA_2$ of sufficient purity rather there is a single sentence suggesting that among the multiple steps involved were affinity and size exclusion chromatography. In the absence of a protocol whereby $cPLA_2$ of sufficient purity can be obtained the claims are not enabled. A second necessary, but not sufficient, condition to practice the invention of claims 16, 18, and 20-25 are crystals of $cPLA_2$. As with the purification scheme the crystallization procedure set forth at page 36 is insufficient to permit reproduction of the crystals. For example no buffer from which $cPLA_2$ is crystallized is set forth not the PEG 1000 or (PEG 400 and DMSO) concentrations necessary to obtain native an heavy atom-modified crystals. Claims 20 and 23 require that one synthesize a potential inhibitor $cPLA_2$, however, the specification fails to set forth teachings which permit the synthesis of molecules which constitute such putative inhibitors. No specific class of molecules with the potential to act as inhibitors is described. Claims 22 and 25 recite particular atoms or amino acids in $cPLA_2$ which may be involved in catalysis. The claims recite that one or more atoms of the recited groups potentially interact with inhibitors, however, the specification merely offers an invitation to experiment to determine which of the recited sites is critical to inhibition.

Applicants respectfully traverse the instant rejection. Applicants assert that one of skill in the art would be able to make and use the invention based on the teachings of the specification and knowledge of the state of the art at the time the application was filed. Applicants submit that the crystal structure coordinates of cytosolic phospholipase A_2 ($cPLA_2$) were deposited at the Brookhaven Protein Data Bank, which is accessible to the

public via, for example, the Internet. The deposit is referred to at page 41 of the specification. Applicants were in possession of the crystal structure coordinates of $cPLA_2$ at the time of filing the instant application. The crystal structure coordinates of $cPLA_2$ clearly enable any person of skill in the art to practice the claimed invention.

In the interest of expediting prosecution, and in no way conceding the validity of the Examiner's position, the specification has been amended to include "Table 2" which includes the structural coordinates of $cPLA_2$, which are contained in the Brookhaven Protein Data Bank as Accession No. 1CJY. Furthermore, the specification has been amended in the interest of the public policy considerations set forth in M.P.E.P. 608.01(p) in order to minimize the public's burden to search for and obtain copies of documents incorporated by reference, *e.g.,* the crystal structure coordinates.

Applicants hereby state that the amendatory material consists of the same material in Brookhaven Protein Data Bank Accession No. 1CJY. The deposit of the coordinates in the Brookhaven Protein Data Bank is referred to on page 41 of the instant specification and incorporated by reference by the statement on page 54 of the instant specification. *No new matter has been added.* The specification has been amended pursuant to 37 C.F.R. §1.52 and 37 C.F.R. §1.58.

Rejection of Claims 16 and 18 Under 35 U.S.C. §112, second paragraph

Claims 16 and 18 have been rejected by the Examiner under 35 U.S.C. §112, second paragraph, as

> being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner is further of the opinion that "Claim 16 should have step (a) amended to recite 'a model of $cPLA_2$ comprising a data set embodying the structure of $cPLA_2$.' Claim 18 is vague in that it does not set forth what $cPLA_2$ is binding.

Applicants respectfully traverse the instant rejection. However, in the interest of expediting prosecution of the instant application and in no way acquiescing to the instant

rejection, Applicants have amended claim 16 in accordance with the Examiner's suggestion.

With respect to claim 18, Applicants have amended claim 18 to recite the term "membrane binding." As stated in the specification, at, for example, page 3, lines 22-25, and page 14, lines 8-22, following activation, $cPLA_2$ translocates to the nuclear membrane and binds with the membrane through interactions between the N-terminal CaLB domain and the membrane. Accordingly, Applicants submit that claim 18, as amended, is clear and definite and would be understood by one of skill in the art when read in combination with the teachings of the specification taken as a whole. Applicants respectfully request reconsideration and withdrawal of the instant 35 U.S.C. §112, second paragraph rejection.

CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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Dated: **March 22, 2002**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace pages 1-52 of the specification with the substitute specification, pages 1-54, provided herewith. A marked-up copy of the specification has been submitted herewith.

In the claims:

Claims 1-15, 17, 19, and 26-29 have been cancelled, without prejudice, and claims 16, 18 have been amended as follows:

16. **(Amended)** A method of identifying a species which is an agonist or antagonist of $cPLA_2$ activity or binding comprising: (a) providing a model of the structure of $cPLA_2$ comprising a data set embodying the structure of $cPLA_2$ ~~the model of claim 8,~~ (b) studying the interaction of candidate species with such model, and (c) selecting a species which is predicted to act as said agonist or antagonist.

18. **(Amended)** A process of identifying a substance that inhibits $cPLA_2$ activity or membrane binding comprising determining the interaction between a candidate substance and a model of the structure of $cPLA_2$.

APPENDIX A

16. A method of identifying a species which is an agonist or antagonist of $cPLA_2$ activity or binding comprising: (a) providing a model of the structure of $cPLA_2$ comprising a data set embodying the structure of $cPLA_2$,(b) studying the interaction of candidate species with such model, and (c) selecting a species which is predicted to act as said agonist or antagonist.

18. A process of identifying a substance that inhibits $cPLA_2$ activity or membrane binding comprising determining the interaction between a candidate substance and a model of the structure of $cPLA_2$.

20. A method of identifying inhibitors of $cPLA_2$ activity by rational drug design comprising:

(a) designing a potential inhibitor that will form non-covalent bonds with one or more amino acids in the $cPLA_2$ active site based upon the crystal structure co-ordinates of $cPLA_2$;

(b) synthesizing the inhibitor; and

(c) determining whether the potential inhibitor inhibits the activity of $cPLA_2$.

21. The method of claim 20 wherein the crystal structure co-ordinates of $cPLA_2$ are obtained from a $cPLA_2$ crystal of space group $P2_12_12$ with a = 153.59 angstroms, b = 95.49 angstroms, and c = 139.13 angstroms.

22. The method of claim 20 wherein said inhibitor is designed to interact with one or more atoms of said one or more amino acids in the $cPLA_2$ active site, and wherein said one or more atoms is selected from the group consisting of:

CB and Oγ atoms of Ser228;

Oδ1and Oδ2 atoms of Asp549 and Asp575;

CB, CG, CD, NE, CZ, NH1 and NH2 atoms of Arg200, Arg413 and Arg579;

Backbone carbonyl oxygen of Trp393;

Nδ2 and Oδ1 atoms of Asn555;

Atoms CD1, CE1, CG, CZ, CE2, and CD2 of Phe397, Phe681, Phe683 and Phe199;

CG, CD1, NE1, CE2, CZ2, CH2, CZ3, CE3 and CD2 of Trp232 and Trp393;

CB and Oγ atoms of Ser577;

Atom s CB and Sγ of Cys331;

Atoms OE1 and OE2 of Glu589;

Atoms CB, CG, CD, CE and NZ of Lys588;

Oγ1 atom of Thr680;

OE1 and OE2 atoms of Glu418 and Glu422;

Atoms CB, CG, SD and CE of Met417;

Atoms CB, CG, CD1 and CD2 of Leu400 and Leu421;

Atoms CB, CG1, CG2, or CD1 of Ile424;

Backbone NH and carbonyl oxygen atoms of Ala578; and

Atoms CB, CG, ND1, CE1, NE2, and CD2 of His639.

23. A method of identifying inhibitors of $cPLA_2$ membrane binding by rational drug design comprising:

(a) designing a potential inhibitor that will form non-covalent bonds with one or more amino acids in the $cPLA_2$ electrostatic patch region based upon the crystal structure co-ordinates of $cPLA_2$;

(b) synthesizing the inhibitor; and

(c) determining whether the potential inhibitor inhibits the membrane binding of $cPLA_2$.

24. The method of claim 23 wherein the crystal structure co-ordinates of $cPLA_2$ are obtained from a $cPLA_2$ crystal of space group $P2_12_12$ with a = 153.59 angstroms, b = 95.49 angstroms, and c = 139.13 angstroms.

25. The method of claim 23 wherein said one or more amino acids are selected from the group consisting of Arg467, Arg485, Lys488, Lys544 and Lys543.